## II. REMARKS

### A. Status of the Claims

Claims 1, 4-20 and 28-30 are currently pending. Claims 21-24, 25-37 and 31-42 were previously cancelled. Claims 2 and 3 have been cancelled herein without prejudice. Claims 1, 11-20 and 28-30 have been amended without prejudice. Support for the amendments can be found in the application as originally filed, e.g. in the claims. It is respectfully submitted that no new matter has been added by virtue of this amendment.

### B. Claim Rejections Under 35 U.S.C. § 103

In the Office Action, claims 1-20, and 28-30 were rejected under 35 U.S.C. §103(a) "as being unpatentable over the combined disclosures of Whitcomb (USPN 6,011,049 hereafter '049) and Byrd et al (USPN 6,191,162 hereafter '162)".

Applicants respectfully submit that the '049 patent in view of the '162 patent, fails to teach or suggest a controlled release oral dosage form which provides a mean time to maximum plasma concentration ($T_{max}$) of an antihyperglycemic drug from 5.5 to 7.5 hours after administration following dinner, as recited in the present claims.

Applicants respectfully disagree with the Examiner's position that the compositions of the '049 patent inherently possess the recited properties directed to a Tmax of from 5.5 to 75 hours. The '049 patent provides a general description of ingredients for dosage forms of their purported invention at column 5, lines 26-34, but does not provide any parameters with respect to the optimization of the general description with respect to particular active agents such as metformin.

In fact, the only particular guidance with respect to metformin formulations suitable for the purported invention of the '049 patent is at column 4, lines 60-61, which states that

metformin "is available in tablets which contain 500 mg and 850 mg of active agent. These can be given up to two times a day or more." Applicants submit that one skilled in the art would recognize that the inventors of the '049 patent are referring to Glucophage® as being suitable for use in their purported invention. Applicants submit herewith Exhibit A, a copy of The Physicians' Desk Reference (PDR), 1998 Edition, pages 795-800, which recites the description of Glucophage, the commercially available formulation for metformin hydrochloride.

The Examiner's attention is directed to page 797, Table 4 of PDR (Exhibit A) which sets forth that the Tmax provided by Glucophage® tablets is from 1.79 to 4.01 hours after administration. Applicants respectfully submit that the lower limit of the claimed Tmax range (i.e. 5.5 hours) is more than 25% of the highest Tmax value (i.e. 4.01 hours) provided by the only specific metformin formulation described in the '049 patent.

Therefore, Applicants respectfully submit that the information in Table 4 of the PDR is evidence that the metformin formulations of the '049 patent cannot be considered to inherently possess the claimed Tmax of 5.5 to 7.5 hours, as the only specific metformin formulation in the '049 patent provides different Tmax values.

The Examiner relies on the '162 patent as teaching "a controlled release formulation capable of reducing serum glucose levels." However, the controlled release formulations described in the '162 patent are with respect to lipoic acid. With respect to metformin, the '162 patent states at column 8, line 42 that "it is preferable to administer metformin (particularly metformin hydrochloride tablets sold as Glucophage®) with controlled release lipoic acid formulations of the present invention.

Therefore, as discussed with respect to the '049 patent, Applicants respectfully submit that page 797, Table 4 of PDR (Exhibit A) is evidence that the metformin formulations of the '062 patent cannot be considered to inherently possess the claimed Tmax of 5.5 to 7.5 hours, as the only specific metformin formulation in the '062 patent provides different Tmax values.

Accordingly, Applicants respectfully submit that the present claims are not obvious over the '049 patent in view of the '162 patent and request that the rejection under 35 U.S.C. § 103(a) be removed.

## III. CONCLUSION

It is respectfully submitted that in view of the arguments presented, this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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antibiotics before parturition, it should
positive Coombs' test may be due to the

**Mutagenesis, and Impairment of Fertility:**
udies have been performed to determine car-
tial. No genetic toxicity tests have been per-

egory B: Reproduction studies have been per-
and rats at doses up to 11 times the human
revealed no evidence of impaired fertility or
m due to cefadroxil monohydrate. There are,
dequate and well controlled studies in preg-
because animal reproduction studies are not
tive of human response, this drug should be
regnancy only if clearly needed.

very:
cefadroxil monohydrate, USP) has not been
during labor and delivery. Treatment should
if clearly needed.

ers:
ould be exercised when cefadroxil monohydrate
to a nursing mother.

Use:

AGE AND ADMINISTRATION)

REACTIONS

ritis
eudomembranous colitis symptoms may occur
ter antibiotic treatment (See WARNINGS). Dys-
rrhea and vomiting have been reported rarely. Di-
also occurred.

ivity
in the form of rash, urticaria, angioedema, and
have been observed. These reactions usually sub-
discontinuation of the drug. Anaphylaxis has
reported.

ctions have included genital pruritus, genital
initis, moderate transient neutropenia, fever,
levations in serum transaminase. Agranulocy-
bocytopenia, erythema multiforme, Stevens-
rome, serum sickness, and arthralgia have
reported.

of the adverse reactions listed above which have
d in patients treated with cefadroxil, the fol-
reactions and altered laboratory tests have
d for cephalosporin-class antibiotics:
rmal necrolysis, abdominal pain, superinfection,
function, toxic nephropathy, hepatic dysfunction
cholestasis, aplastic anemia, hemolytic anemia,
prolonged prothrombin time, positive Coombs
d BUN, increased creatinine, elevated alkaline
elevated aspartate aminotransferase (AST),
e aminotransferase (ALT), elevated bilirubin,
eosinophilia, pancytopenia, neutropenia.
osporins have been implicated in triggering
cularly in patients with renal impairment,
age was not reduced (see DOSAGE AND AD-
ATION and OVERDOSAGE). If seizures associ-
g therapy occur, the drug should be discontin-
vulsant therapy can be given if clinically indi-

children under six years of age suggested that
less than 250 mg/kg of cephalosporins is not as-
significant outcomes. No action is required
general support and observation. For amounts
250 mg/kg, induce gastric emptying.
patients, it was demonstrated that an average
g oral dose is extracted from the body during a
hemodialysis session.

AGE AND ADMINISTRATION
acid-stable and may be administered orally
regard to meals. Administration with food may be
diminishing potential gastrointestinal complaints
associated with oral cephalosporin therapy.

**Tract Infections:** For uncomplicated lower uri-
nfections (ie, cystitis) the usual dosage is 1 or 2 g
ingle (q.d.) or divided doses (b.i.d.).
urinary tract infections the usual dosage is 2 g
divided doses (b.i.d.).
**Skin Structure Infections:** For skin and skin
nfections the usual dosage is 1 g per day in single
ivided doses (b.i.d.).
**itis and Tonsillitis:** Treatment of group A beta-
streptococcal pharyngitis and tonsillitis — 1 g per
(q.d.) or divided doses (b.i.d.) for 10 days.

tract infections, the recommended daily dosage
is 30 mg/kg/day in divided doses every 12 hours.
ital tonsillitis, and impetigo, the recommended
for children is 30 mg/kg/day in a single dose or
divided doses every 12 hours. For other skin and skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of DURICEF® should be administered for at least 10 days.

See chart for total daily dosage for children.

[See first table above]

In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of DURICEF (cefadroxil monohydrate, USP) and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 $M^2$]) is 500 mg at the time intervals listed below.

| Creatinine Clearances | Dosage Interval |
|---|---|
| 0-10 mL/min | 36 hours |
| 10-25 mL/min | 24 hours |
| 25-50 mL/min | 12 hours |

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

[See second table above]

## HOW SUPPLIED

DURICEF® (cefadroxil monohydrate, USP) 500 mg Capsules: opaque, maroon and white hard gelatin capsules, imprinted with "PPP" and "784" on one end and with "DURICEF" and "500 mg" on the other end. Capsules are supplied as follows:

| | |
|---|---|
| **NDC** 0087-0784-07 | Bottle of 20 |
| **NDC** 0087-0784-46 | Bottle of 50 |
| **NDC** 0087-0784-42 | Bottle of 100 |
| **NDC** 0087-0784-44 | 10 strips of 10 individually labeled blisters with 1 capsule per blister |

Store at controlled room temperature (15°–30°C).

DURICEF® (cefadroxil monohydrate, USP) 1 gram Tablets: white to off white, top bisected, oval shaped, imprinted with "PPP" on one side of the bisect and "785" on the other side of the bisect. Tablets are supplied as follows:

| | |
|---|---|
| **NDC** 0087-0785-43 | Bottle of 50 |
| **NDC** 0087-0785-42 | Bottle of 100 |
| **NDC** 0087-0785-44 | 10 strips of 10 individually labeled blisters with 1 tablet per blister |
| **NDC** 0087-0785-45 | 4 packs of 10 individually labeled blisters with 1 tablet per blister |

Store at controlled room temperature (15°–30°C).

DURICEF® for Oral Suspension is orange-pineapple flavored, and is supplied as follows:

| | | |
|---|---|---|
| 125 mg/5 mL | **NDC** 0087-0786-42 | 50 mL Bottle |
| | **NDC** 0087-0786-41 | 100 mL Bottle |
| 250 mg/5 mL | **NDC** 0087-0782-42 | 50 mL Bottle |
| | **NDC** 0087-0782-41 | 100 mL Bottle |
| 500 mg/5 mL | **NDC** 0087-0783-42 | 50 mL Bottle |
| | **NDC** 0087-0783-05 | 75 mL Bottle |
| | **NDC** 0087-0783-41 | 100 mL Bottle |

Prior to reconstitution: Store at controlled room temperature (15°–30°C).

**DAILY DOSAGE OF DURICEF® SUSPENSION**

| Child's Weight | | | | |
|---|---|---|---|---|
| lbs | kg | 125 mg/5 mL | 250 mg/5 mL | 500 mg/5 mL |
| 10 | 4.5 | 1 tsp | — | |
| 20 | 9.1 | 2 tsp | 1 tsp | |
| 30 | 13.6 | 3 tsp | 1½ tsp | |
| 40 | 18.2 | 4 tsp | 2 tsp | 1 tsp |
| 50 | 22.7 | 5 tsp | 2½ tsp | 1¼ tsp |
| 60 | 27.3 | 6 tsp | 3 tsp | 1½ tsp |
| 70 & above | 31.8+ | — | — | 2 tsp |

**Reconstitution Directions for Oral Suspension**

| Bottle Size | Reconstitution Directions |
|---|---|
| 100 mL | Suspend in a total of 67 mL water. Method: Tap bottle lightly to loosen powder. Add 67 mL of water in two portions. Shake well after each addition. |
| 75 mL | Suspend in a total of 51 mL water. Method: Tap bottle lightly to loosen powder. Add 51 mL of water in two portions. Shake well after each addition. |
| 50 mL | Suspend in a total of 34 mL water. Method: Tap bottle lightly to loosen powder. Add 34 mL of water in two portions. Shake well after each addition. |

After reconstitution, store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.


U.S. Patent Nos. 4,160,863
4,504,657

## REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test*, 4th Edition, Vol. 10 (7): M2-A4, Villanova, PA, April, 1990.
2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 10 (8): M7-A2, Villanova, PA, April, 1990.



0783DIM-05 Revised February 1997
E3-B001-2-97



*Shown in Product Identification Guide, page 307*


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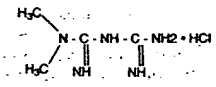
# GLUCOPHAGE® ℞

*[glü-kō-faj ]*

**(metformin hydrochloride tablets)**

## DESCRIPTION

GLUCOPHAGE (metformin hydrochloride tablets) is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to the oral sulfonylureas. The structural formula is as shown:




Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether or chloroform. The $pK_a$ of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg and 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

## CLINICAL PHARMACOLOGY

**Antidiabetic Activity**

GLUCOPHAGE is an antihyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. GLUCOPHAGE decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, GLUCOPHAGE does not


***Continued on next page***

## lucophage—Cont.

duce hypoglycemia in either diabetic or nondiabetic subs (except in special circumstances, see PRECAUTIONS) l does not cause hyperinsulinemia. With metformin ther-, insulin secretion remains unchanged while fasting in- in levels and day-long plasma insulin response may ac- lly decrease.

a double-blind, placebo-controlled, multicenter U.S. clin- l trial involving obese NIDDM patients whose hyperglyc- nia was not adequately controlled with dietary manage- nt alone (baseline fasting plasma glucose [FPG] of ap- oximately 240 mg/dL), treatment with GLUCOPHAGE to 2.55 g/day) for 29 weeks resulted in significant mean reduction in fasting and postprandial plasma glucose G) and $HbA_{1c}$ of 59 mg/dL, 83 mg/dL, and 1.8%, respec- ely, compared to placebo group (see Table 1).

**Table 1. GLUCOPHAGE vs Placebo Summary of Mean Changes from Baseline* in Plasma Glucose $HbA_{1c}$ and Body Weight, at Final Visit (29-week study)**

| | GLUCOPHAGE (n =141) | Placebo (n=145) | P-Value |
|---|---|---|---|
| **G (mg/dL)** | | | |
| seline | 241.5 | 237.7 | NS |
| ange at INAL VISIT | −53.0 | 6.3 | 0.001 ** |
| **moglobin $A_{1c}$(%)** | | | |
| seline | 8.4 | 8.2 | NS |
| ange at INAL VISIT | −1.4 | 0.4 | 0.001 ** |
| **dy Weight (lbs)** | | | |
| seline | 201.0 | 206.0 | NS |
| ange at INAL VISIT | −1.4 | −2.4 | NS |

All patients on diet therapy at Baseline
Statistically significant

onotherapy with GLUCOPHAGE may be effective in pa- nts who have not responded to sulfonylureas or who have ly a partial response to sulfonylureas or who have ceased respond to sulfonylureas. In such patients, if adequate ycemic control is not attained with GLUCOPHAGE mono- erapy, the combination of GLUCOPHAGE and a sulfonyl- ea may have a synergistic effect, since both agents act to prove glucose tolerance by different but complimentary echanisms.

29-week, double-blind, placebo-controlled study of GLU- OPHAGE and glyburide, alone and in combination, was nducted in obese NIDDM patients who had failed to hieve adequate glycemic control while on maximum doses glyburide (baseline FPG of approximately 250 mg/dL) ee Table 2). Patients randomized to continue on gluburide perienced worsening of glycemic control, with mean in- eases in FPG, PPG and $HbA_{1c}$ of 14 mg/dL, 3 mg/dL and .2%, respectively. In contrast, those randomized to GLU- OPHAGE (metformin hydrochloride tablets) (up to 2.5 /day) did not experience a deterioration in glycemic con- ol, but rather a slight improvement, with mean reductions FPG, PPG and $HbA_{1c}$ of 1 mg/dL, 6 mg/dL and 0.4%, re- pectively. The combination of GLUCOPHAGE and gly- uride was synergistic in reducing FPG, PPG and $HbA_{1c}$ evels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Com- ared to the results of glyburide treatment alone, the net ifferences with combined treatment were −77 mg/dL, −68 g/dL and −1.9%, respectively (see Table 2).

See table above]

he magnitude of the decline in fasting blood glucose con- entration following the institution of GLUCOPHAGE (met- ormin hydrochloride tablets) therapy is proportional to the evel of fasting hyperglycemia. Non-insulin-dependent dia- etics with higher fasting glucose concentrations will expe- ience greater declines in plasma glucose and glycosylated emoglobin.

LUCOPHAGE has a modest favorable effect on serum lip- ds, which are often abnormal in NIDDM patients. In clini- al studies, particularly when baseline levels were abnor- nally elevated, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycer- des, total cholesterol and LDL cholesterol levels and had no dverse effects on other lipid levels (see Table 3).

See table above]

n contrast to sulfonylureas, body weight of individuals on LUCOPHAGE tends to remain stable or may even de- rease somewhat (see Table 1 and 2).

n summary, metformin-treated patients showed significant mprovement in all parameters of glycemic control (FPG; PPG and $HbA_{1c}$), stabilization or decrease in body weight, nd a tendency to improvement in the lipid profile, particu- larly when baseline values are abnormally elevated.

**Pharmacokinetics**

**Absorption and Bioavailability:**

The absolute bioavailability of a 500 mg metformin hydro- chloride tablet given under fasting conditions is approxi-

**Table 2. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or Glucophage (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Plasma Glucose, $HbA_{1c}$ and Body Weight, at Final Visit (29-week study)**

| | Comb (n =213) | Glyb (n =209) | GLU (n =210) | P-values Glyb vs Comb | P-values GLU vs Comb | GLU |
|---|---|---|---|---|---|---|
| **Fasting Plasma Glucose (mg/dL)** | | | | | | |
| Baseline | 250.5 | 247.5 | 253.9 | NS | NS | NS |
| Change at FINAL VISIT | −63.5 | 13.7 | −0.9 | 0.001 ** | 0.001 ** | 0.025 |
| **Hemoglobin $A_{1c}$ (%)** | | | | | | |
| Baseline | 8.8 | 8.5 | 8.9 | NS | NS | 0.007 |
| Change at FINAL VISIT | −1.7 | 0.2 | −0.4 | 0.001 ** | 0.001 ** | 0.001 |
| **Body Weight (lbs)** | | | | | | |
| Baseline | 202.2 | 203.0 | 204.0 | NS | NS | NS |
| Change at FINAL VISIT | 0.9 | −0.7 | −8.4 | 0.011 ** | 0.001 ** | 0.001 |

* All patients of glyburide, 20 mg/day, at Baseline
** Statistically significant

**Table 3. Summary of Mean Percent Reduction of Major Serum Lipid Variables at Final Visit (29-week study)**

| | Glucophage vs. Placebo (% Change from Baseline) | | Combined Glucophage/Glyburide vs. Monotherapy (% Change from Baseline) | | |
|---|---|---|---|---|---|
| | Glucophage (n =141) | Placebo (n =145) | Glucophage (n =210) | Glucophage/ Glyburide (n =213) | Glybur (n =209 |
| Total Cholesterol | − 5%* | 1% | − 2% | − 4%** | |
| Total Triglycerides | − 16% | 1% | − 3%** | − 8%** | |
| LDL-Cholesterol | − 8%* | 1% | − 4%** | − 6%** | |
| HDL-Cholesterol | 2% | − 1% | 5% | 3% | |

* <0.05 vs. Placebo
** <0.05 vs. Glyburide

mately 50–60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

**Distribution:**

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE (metformin hydrochloride tablets), steady state plasma concentrations of metformin are reached within 24–48 hours and are generally <1 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

**Metabolism and Elimination:**

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

**Special Populations:**

**NIDDM Subjects:**

In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between diabetics and nondiabe 4), nor is there any accumulation of metfo group at usual clinical doses.

**Renal Insufficiency:**

In subjects with decreased renal function sured creatinine clearance), the plasma of metformin is prolonged and the renal creased in proportion to the decrease in creat (see Table 4).

**Hepatic Insufficiency:**

No pharmacokinetic studies have been jects with hepatic insufficiency.

**Geriatrics:**

Limited data from controlled pharmacok metformin in healthy elderly subjects (65 plasma clearance is decreased, the half-life $C_{max}$ is increased, compared to healthy From these data, it appears that the change pharmacokinetics with aging is primarily change in renal function (see Table 4).

[See table at top of next page]

**Pediatrics:**

No pharmacokinetic studies have been conduc ric subjects.

**Gender:**

Metformin pharmacokinetic parameters di nificantly in diabetic and nondiabetic subj lyzed according to gender (males=191, fem larly, in controlled clinical studies in patient the antihyperglycemic effect of GLUCOPH hydrochloride tablets) was comparable in males.

**Race:**

No studies of metformin pharmacokinet cording to race have been performed. In studies of GLUCOPHAGE in patients with tihyperglycemic effect was comparable in blacks (n=51) and hispanics (n=24).

## INDICATIONS AND USE

GLUCOPHAGE (metformin hydroch monotherapy, is indicated as an adju blood glucose in patients with NIDDM mia cannot be satisfactorily managed

GLUCOPHAGE may be used concomitantly with a sulfonylurea, diet, and GLUCOPHAGE or a sulfonylurea alone in patients with inadequate glycemic control.

As initial treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. Fasting blood glucose control in diet-managed patients may be labile, thus requiring only short-term pharmacologic support. The importance of regular physical activity should be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If adequate management program fails to reduce symptoms and/or fasting glucose, the use of GLUCOPHAGE alone or GLUCOPHAGE plus a sulfonylurea should be considered.

After a suitable trial of such treatments, glucose control cannot be achieved, consideration should be given to therapy with insulin. Judgments should be based on regular periodic laboratory evaluations.

## CONTRAINDICATIONS

GLUCOPHAGE is contraindicated in patients with:

- renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
- GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because such products may result in acute alteration of renal function (See also PRECAUTIONS).
- hypersensitivity to metformin hydrochloride.
- acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

## WARNINGS

**Lactic Acidosis:**

**Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathologic conditions, including diabetes mellitus, whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.**

**The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately no fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by the use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Since impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE (metformin hydrochloride tablets) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, while taking GLUCOPHAGE (metformin hydrochloride tablets), since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and during any surgical procedure (see also PRECAUTIONS).**

**The risk of lactic acidosis often is subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.**

**Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)**

**Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).**

**Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).**

**SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:**

**The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 1027 patients who were randomly assigned to one of five treatment groups (*Diabetes*, 19 (Suppl.2):747–830, 1970; *Diabetes*, 24 (Suppl.1):65–184, 1975).**

**The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or diet plus a fixed dose of phenformin (100 mg per day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. Total mortality was increased in both the tolbutamide- and phenformin-treated groups and this increase was statistically significant in the phenformin-treated group. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of GLUCOPHAGE and alternative modes of therapy.**

**Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related oral antidiabetic drugs, in view of the similarities in mode of action and chemical structure among these drugs in each category.**

Table 4. Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

| Subject Groups: GLUCOPHAGE dose[a] (number of subjects) | $C_{max}$[b] (µg/mL) | $t_{max}$[c] (hrs) | Renal Clearance (mL/min) |
|---|---|---|---|
| **Healthy, nondiabetic adults:** | | | |
| 500 mg SD[d](24) | 1.03 (±0.33) | 2.75 (±0.81) | 600 (±132) |
| 850 mg SD (74)[e] | 1.60 (±0.38) | 2.64 (±0.82) | 552 (±139) |
| 850 mg t.i.d. for 19 doses[f] (9) | 2.01 (±0.42) | 1.79 (±0.94) | 642 (±173) |
| **Adults with NIDDM:** | | | |
| 850 mg SD (23) | 1.48 (±0.5) | 3.32 (±1.08) | 491 (±138) |
| 850 mg t.i.d. for 19 doses[f] (9) | 1.90 (±0.62) | 2.01 (±1.22) | 550 (±160) |
| **Elderly[g], healthy nondiabetic adults:** | | | |
| 850 mg SD (12) | 2.45 (±0.70) | 2.71 (±1.05) | 412 (±98) |
| **Renal-impaired adults: 850 mg SD** | | | |
| Mild ($CL_{cr}$[h] 61–90 mL/min) (5) | 1.86 (±0.52) | 3.20 (±0.45) | 384 (±122) |
| Moderate ($CL_{cr}$ 31–60 mL/min) (4) | 4.12 (±1.83) | 3.75 (±0.50) | 108 (±57) |
| Severe ($CL_{cr}$ 10–30 mL/min) (6) | 3.93 (±0.92) | 4.01 (±1.10) | 130 (±90) |

[a]–All doses given fasting except the first 18 doses of the multiple dose studies;
[b]–Peak plasma concentration;
[c]–Time to peak plasma concentration;
[d]–SD=single dose;
[e]–Combined results (average means) of five studies: mean age 32 years (range 23–59 yrs).
[f]–Kinetic study done following dose 19, given fasting.
[g]–Elderly subjects, mean age 71 years (range 65–81 years).
[h]–$CL_{cr}$=creatinine clearance normalized to body surface area of 1.73 $m^2$.

## PRECAUTIONS

**General:**

**Monitoring of renal function**—GLUCOPHAGE is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION).

Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present.

**Use of concomitant medications that may affect renal function or metformin disposition**—Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See Drug Interactions), should be used with caution.

**Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials)**—Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

**Hypoxic states**—Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued.

**Surgical procedures**—GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids ) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

**Alcohol intake**—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE.

*Continued on next page*

## Glucophage—Cont.

**Impaired hepatic function**—Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

**Vitamin $B_{12}$ levels**—A decrease to subnormal levels of previously normal serum vitamin $B_{12}$ levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with $B_{12}$ absorption from the $B_{12}$-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE (metformin hydrochloride tablets) or vitamin $B_{12}$ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin $B_{12}$ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin $B_{12}$ levels. In these patients, routine serum vitamin $B_{12}$ measurements at two- to three-year intervals may be useful.

**Change in clinical status of previously controlled diabetic**—A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

**Hypoglycemia**—Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

**Loss of control of blood glucose**—When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE (metformin hydrochloride tablets) and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

**Information for Patients:**

Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE.

GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

(See Patient Labeling Printed Below)

**Laboratory Tests:**

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE (metformin hydrochloride tablets) therapy, if this is suspected, vitamin $B_{12}$ deficiency should be excluded.

**Drug Interactions:**

**Glyburide:** In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and $C_{max}$ were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy).

**Furosemide:** A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood $C_{max}$ by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the $C_{max}$ and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

**Nifedipine:** A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin $C_{max}$ and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. $T_{max}$ and half-life were unaffected. Nifedipine appears to enhance the absorption metformin. Metformin had minimal effects on nifedipine.

**Cationic Drugs:** Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

**Other:** Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and Ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential to metf found in the Ames test (*S. typhimurium*), gene test (mouse lymphoma cells), chromosomal aberra (human lymphocytes), or *in-vivo* micronuclei for (mouse bone marrow).

Fertility of male or female rats was unaffected by administration at doses as high as 600 mg/kg/d proximately two times the maximum recommend daily dose on a body surface area basis.

**Pregnancy:**

**Teratogenic effects:**

**Pregnancy Category B.** Safety in pregnant women been established. Metformin was not teratogenic in rabbits at doses up to 600 mg/kg/day, or about two maximum recommended human daily dose on a face area basis. Determination of fetal concentra onstrated a partial placental barrier to metformin animal reproduction studies are not always predi man response, any decision to use this drug shou anced against the benefits and risks.

Because recent information suggests that abnor glucose levels during pregnancy are associate higher incidence of congenital abnormalities, the sensus among experts that insulin be used dur nancy to maintain blood glucose levels as close to possible.

**Nursing Mothers:**

Studies in lactating rats show that metformin into milk and reaches levels comparable to those Similar studies have not been conducted in nurs ers, but caution should be exercised in such pat decision should be made whether to discontinue to discontinue the drug, taking into account the of the drug to the mother.

**Pediatric Use:**

Safety and effectiveness in pediatric patients have established. Studies in maturity-onset diabetes (MODY) have not been conducted.

**Geriatric Use:**

Controlled clinical studies of GLUCOPHAGE hydrochloride tablets) did not include sufficient elderly patients to determine whether they res ently from younger patients, although other rep cal experience has not identified differences in re tween the elderly and younger patients. GLUCO known to be substantially excreted by the kidn cause the risk of serious adverse reactions to greater in patients with impaired renal function only be used in patients with normal renal fun CONTRAINDICATIONS, CLINICAL PHARM Pharmacokinetics). Because aging is associat duced renal function, GLUCOPHAGE should caution as age increases. Care should be taken lection and should be based on careful and regul ing of renal function. Generally, elderly patien be titrated to the maximum dose of GLUCO also DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS

**Lactic Acidosis:** See WARNINGS, PRECA OVERDOSAGE Sections.

**Gastrointestinal Reactions:** Gastrointestinal (diarrhea, nausea, vomiting, abdominal bloating and anorexia) are the most common reactions COPHAGE and are approximately 30% incre patients on GLUCOPHAGE monotherapy than treated patients, particularly during initiation COPHAGE therapy. These symptoms are gen sient and resolve spontaneously during contin ment. Occasionally, temporary dose reductio useful. In controlled trials, GLUCOPHAGE was ued due to gastrointestinal reactions in approxim patients.

Because gastrointestinal symptoms during ini tion appear to be dose-related, they may be gradual dose escalation and by having patient COPHAGE (metformin hydrochloride tablets) (see DOSAGE and ADMINISTRATION).

Because significant diarrhea and/or vomiting hydration and prerenal azotemia, under sta stances, GLUCOPHAGE should be temporar ued.

For patients who have been stabilized on GL nonspecific gastrointestinal symptoms should uted to therapy unless intercurrent illness have been excluded.

**Special Senses:** During initiation of GLUC apy, approximately 3% of patients may e pleasant or metallic taste, which usually res ously.

**Dermatologic Reactions:** The incidence of in controlled clinical trials was comparable GLUCOPHAGE monotherapy and to sulfony COPHAGE/sulfonylurea therapy.

logic: (See also PRECAUTIONS). During con- clinical trials of 29 weeks duration, approximately patients on GLUCOPHAGE monotherapy and 6% of ents on GLUCOPHAGE/sulfonylurea therapy developed mptomatic subnormal serum vitamin $B_{12}$ levels; serum and levels did not decrease significantly. However, only cases of megaloblastic anemia have been reported with formin administration (none during U.S. clinical studand no increased incidence of neuropathy has been obTherefore, serum $B_{12}$ levels should be appropriately nitored or periodic parenteral $B_{12}$ supplementation con- ered.

**DRUG ABUSE AND DEPENDENCE**

GLUCOPHAGE possesses no pharmacodynamic properties, primary or secondary, which could be expected to re- abuse as a recreational drug or addiction.

**OVERDOSAGE**

Hypoglycemia has not been seen with ingestion of up to 85 ams of GLUCOPHAGE, although lactic acidosis has oc- ed in such circumstances (see WARNINGS). Metformin dialyzable with a clearance of up to 170 mL/min under d hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in hom metformin overdosage is suspected.

**DOSAGE AND ADMINISTRATION**

There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE or any other pharmacologic agent. Dosage of GLUCOPHAGE must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. GLUCOPHAGE should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below, INITIAL STARTING DOSE), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE and identify the minimum effective dose for the patient thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE either when used as monotherapy or in combination with sulfonylurea.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate reduction of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Concomitant administration of GLUCOPHAGE (metformin hydrochloride tablets) may be sufficient during periods of instability of control in patients usually well-controlled on diet alone.

**Usual Starting Dose:**

In general clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

**GLUCOPHAGE 500 mg Tablets:**

The usual starting dose of GLUCOPHAGE 500 mg tablets is one tablet given with the morning and evening meals. Dosage increases should be made in increments of one tablet every week given in divided doses, up to a maximum of 2000 mg per day. GLUCOPHAGE can be administered twice a day up to 2000 mg per day (e.g., 1000 mg b.i.d. with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given t.i.d. with meals.

**GLUCOPHAGE 850 mg Tablets:**

The usual starting dose of GLUCOPHAGE 850 mg tablets is one tablet daily given with the morning meal. Dosage increases should be made in increments of one tablet every week given in divided doses, up to a maximum of 2550 mg per day. The usual maintenance dose is 850 mg two to three times daily with the morning and evening meals. When necessary, it may be given 850 mg t.i.d. with meals.

**Transfer From Other Antidiabetic Therapy:**

When transferring patients from standard oral hypoglycemic agents, other than chlorpropamide to GLUCOPHAGE, no transition period generally is necessary. While transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

**Concomitant GLUCOPHAGE and Oral Sulfonylurea Therapy:**

If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration may be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE at the maximum dose, in patients with primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide). Published clinical information exists for the use of metformin with either chlorpropamide, tolbutamide or glipizide. No published clinical information exists regarding concomitant use of metformin with acetohexamide or tolazamide.

With concomitant GLUCOPHAGE and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea).

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE and the maximum dose of an oral sulfonylurea, institution of insulin therapy and discontinuation of these oral agents should be considered.

**Specific Patient Populations:**

GLUCOPHAGE is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of GLUCOPHAGE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE.

In debilitated or malnourished patients, the dosing should also be conservative and based on a careful assessment of renal function.

**HOW SUPPLIED**

GLUCOPHAGE® (brand of metformin hydrochloride tablets) is supplied as white, round, white to off-white, film-coated tablets, available in the following strengths:

| | | |
|---|---|---|
| 500 mg | Bottles of 100 | NDC 0087-6060-05 |
| 850 mg | Bottles of 100 | NDC 0087-6070-05 |

GLUCOPHAGE 500 mg tablets are debossed with BMS 6060 around the periphery of the tablet on one side and 500 across the face of the other side. GLUCOPHAGE 850 mg tablets are debossed with BMS 6070 around the periphery of the tablet on one side and 850 across the face of the other side.

**Storage**

Store between 15°–30°C (59°–86°F).

**PATIENT INFORMATION ABOUT GLUCOPHAGE® (metformin hydrochloride tablets)**

**500 mg and 850 mg**

**WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 7–11)**

**Q1. Why do I need to take GLUCOPHAGE?**

Your doctor has prescribed GLUCOPHAGE (GLUE-coe-fahj) to treat your type II diabetes. This is also known as non-insulin-dependent diabetes mellitus (NIDDM).

**Q2. What is type II diabetes?**

People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

**Q3. How is type II diabetes usually controlled?**

High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

**Q4. Does GLUCOPHAGE work differently from other glucose-control medications?**

Yes it does. Until GLUCOPHAGE was introduced, all the available oral glucose-control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE (metformin hydrochloride tablets) lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

**Q5. What happens if my blood sugar is still too high?**

When blood sugar cannot be lowered enough by either GLUCOPHAGE (metformin hydrochloride tablets) or a sulfonylurea, the two me... However, if you ... with diet, exerci... orally, then your ... control your diabe...

**Q6. Can GLUCOPHAGE, li... can cause side effe... effects are minor a... COPHAGE for a wh... rare side effects rel...**

**Q7. What kind of ...**

If side effects occur, ... weeks in therapy. Th... such as arrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects. Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one-third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problem does come back or start later on during the therapy.

About three out of one hundred people report having a temporary unpleasant or metallic taste when they start taking GLUCOPHAGE.

**Q8. Are there any serious side effects that GLUCOPHAGE can cause?**

GLUCOPHAGE rarely causes serious side effects. The most serious side effect that GLUCOPHAGE can cause is called lactic acidosis.

**Q9. What is lactic acidosis and can it happen to me?**

Lacitic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with GLUCOPHAGE is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported about one in 33,000 patients taking GLUCOPHAGE over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It is also important for your liver to be working normally when you take GLUCOPHAGE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOPHAGE causes harm to the kidneys or liver.

**Q10. Are there other risk factors for lactic acidosis?**

Your risk of developing lactic acidosis from taking GLUCOPHAGE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should not take GLUCOPHAGE if:

- You have chronic kidney or liver problems
- You drink alcohol excessively (all the time or short-term "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, severe infection, or a stroke.

**Q11. What are the symptoms of lactic acidosis?**

Some of the symptoms include: feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing; unusual or unexpected stomach discomfort, feeling cold, dizziness or lightheaded, or suddenly developing slow or irregular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOPHAGE and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

**Q12. What does my doctor need to know to decrease the risk of lactic acidosis?**

Tell your doctor if you have an illness that results in severe vomiting, diarrhea and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking GLUCOPHAGE temporarily.

You should let your doctor know if you are going to have surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOPHAGE therapy will need to be stopped temporarily in such instances.

**Q13. Can I take GLUCOPHAGE with other medications?**

Remind your doctor that you are taking GLUCOPHAGE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOPHAGE may interfere with the way some drugs work and drugs may interfere with the action of GLUCOPHAGE.

***Continued on next p***

## Glucophage—Cont.

**Q14. What if I become pregnant while taking GLUCOPHAGE?**
Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take GLUCOPHAGE during pregnancy.
Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOPHAGE if you are nursing a child.
**Q15. Are there other risks associated with GLUCOPHAGE?**
There is some evidence that any oral diabetes drug may increase the risk of heart problems. Experts are not sure what the real risk for heart problems, if any, from taking oral diabetes medicine.
**Q16. How do I take GLUCOPHAGE?**
Your doctor will tell you how many GLUCOPHAGE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOPHAGE and your dosage will be increased gradually until your blood sugar is controlled.
**Q17. Where can I get more information about GLUCOPHAGE?**
This leaflet is a summary of the most important information about GLUCOPHAGE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type II diabetes as well as GLUCOPHAGE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.
Glucophage is a registered trademark of LIPHA s.a.
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6060 DIM-01 Revised: June 1996
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*Shown in Product Identification Guide, page 307*

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## MAXIPIME®

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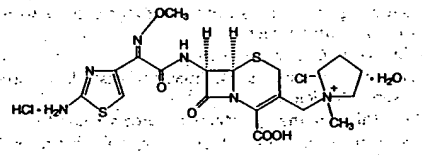
*[max-i-pime]*
**(Cefepime Hydrochloride) for Injection**
**For Intravenous or Intramuscular Use**

**CAUTION: Federal law prohibits dispensing without prescription.**

### DESCRIPTION

Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(Z)- (*O*-methyloxime), monohydrochloride, monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride is a white to pale yellow powder with a molecular formula of $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ and a molecular weight of 571.5. It is highly soluble in water.
MAXIPIME® (cefepime hydrochloride) for Injection, is supplied for intramuscular or intravenous administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. (See **DOSAGE AND ADMINISTRATION**.) MAXIPIME is a sterile, dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of .725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0-6.0. Freshly constituted solutions of MAXIPIME will range in color from colorless to amber.

### CLINICAL PHARMACOLOGY

**Pharmacokinetics**
The average plasma concentrations of cefepime observed in healthy adult male volunteers (n = 9) at various times following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in Table 1. Elimination of cefepime is principally via renal excretion with an average (± SD) half-life of 2.0 (± 0.3) hours and total body clearance of 120.0 (± 8.0) mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n = 7) receiving clinically relevant doses for a period of 9 days.

TABLE 3

**Average Concentrations of Cefepime in Specific Body Fluids (µg/mL) or Tissues (µg/g)**

| Tissue or Fluid | Dose/Route | # of Patients | Average Time of Sample Post-Dose (hr) | Average Concentration |
|---|---|---|---|---|
| Blister Fluid | 2 g IV | 6 | 1.5 | 81.4 µg/mL |
| Bronchial Mucosa | 2 g IV | 20 | 4.8 | 24.1 µg/g |
| Sputum | 2 g IV | 5 | 4.0 | 7.4 µg/mL |
| Urine | 500 mg IV | 8 | 0-4 | 292 µg/mL |
| | 1 g IV | 12 | 0-4 | 926 µg/mL |
| | 2 g IV | 12 | 0-4 | 3120 µg/mL |

**Absorption**
The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous administration are portrayed in Table 1.

TABLE 1

**Average Plasma Concentrations in µg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intravenous Administration**

| | MAXIPIME | | |
|---|---|---|---|
| Parameter | 500 mg IV | 1 g IV | 2 g IV |
| 0.5 hr | 38.2 | 78.7 | 163.1 |
| 1.0 hr | 21.6 | 44.5 | 85.8 |
| 2.0 hr | 11.6 | 24.3 | 44.8 |
| 4.0 hr | 5.0 | 10.5 | 19.2 |
| 8.0 hr | 1.4 | 2.4 | 3.9 |
| 12.0 hr | 0.2 | 0.6 | 1.1 |
| $C_{max}$, µg/mL | 39.1 (3.5) | 81.7 (5.1) | 163.9 (25.3) |
| AUC, hr•µg/mL | 70.8 (6.7) | 148.5 (15.1) | 284.8 (30.6) |
| Number of subjects (male) | 9 | 9 | 9 |

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized in Table 2. The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g IM and do not vary with respect to treatment duration.

TABLE 2

**Average Plasma Concentrations in µg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intramuscular Administration**

| | MAXIPIME (cefepime hydrochloride) | | |
|---|---|---|---|
| Parameter | 500 mg IM | 1 g IM | 2 g IM |
| 0.5 hr | 8.2 | 14.8 | 36.1 |
| 1.0 hr | 12.5 | 25.9 | 49.9 |
| 2.0 hr | 12.0 | 26.3 | 51.3 |
| 4.0 hr | 6.9 | 16.0 | 31.5 |
| 8.0 hr | 1.9 | 4.5 | 8.7 |
| 12.0 hr | 0.7 | 1.4 | 2.3 |
| $C_{max}$, µg/mL | 13.9 (3.4) | 29.6 (4.4) | 57.5 (9.5) |
| $T_{max}$, hr | 1.4 (0.9) | 1.6 (0.4) | 1.5 (0.4) |
| AUC, hr•µg/mL | 60.0 (8.0) | 137.0 (11.0) | 262.0 (23.0) |
| Number of subjects (male) | 6 | 6 | 12 |

**Distribution**
The average steady state volume of distribution of cefepime is 18.0 (± 2.0)L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.
Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day. (See **PRECAUTIONS, Nursing Mothers**.)
Concentrations of cefepime achieved in specific tissue and body fluids are listed in Table 3.
[See table above]
Data suggest that cefepime does cross the inflamed blood brain barrier. The clinical relevance of these data remain at this time.
**Metabolism and Excretion**
Cefepime is metabolized to N-methylpyrrolidine (NMP), which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 30% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See **DOSAGE AND ADMINISTRATION**.)
**Special Populations**
*Geriatric patients:* Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men (n = 12) and women (n = 12) whose creatinine clearance was 74.0 (± 15.0) mL/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less. (See **DOSAGE AND ADMINISTRATION**.)
*Renal Insufficiency:* Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency (n = 30). The average half-life in patients undergoing hemodialysis was 13.5 (± 2.7) hours and in patients undergoing continuous peritoneal dialysis was 19.0 (± 2.1) hours. Cefepime total body clearance decreased proportionately with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients. (See **DOSAGE AND ADMINISTRATION**.)
*Hepatic Insufficiency:* The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose (n = 11).
**Microbiology**
Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has been shown to have a spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram-negative bacterial cells. Within bacterial cells, the most prominent targets of cefepime are the penicillin binding proteins (PBPs).
Cefepime has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.
Aerobic Gram-Negative Microorganisms:
*Enterobacter*
*Escherichia coli*
*Klebsiella pneumoniae*
*Proteus mirabilis*
*Pseudomonas aeruginosa*
Aerobic Gram-Positive Microorganisms:
*Staphylococcus aureus* (methicillin-susceptible strains only)